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SOME CONTRIBUTIONS FROM THE SISTER SCIENCES

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No branch of science or art furnishes a more striking example than does medicine of the fact that increasing specialization is necessarily accompanied by increasing interdependence and cooperation among the specialized fields. In the early days all the sciences were combined together, frequently in the same individual. Later the various specialties had a tendency to run their separate courses. Now we find them coming together again for mutual support. It is something like the story of the prodigal son, who, after the adventures of an independent career, is glad to come back again to his family.

This is well illustrated by the development of the significance of the word "physics," which in the original Greek meant "that which pertains to nature." It was used to designate those phenomena of the natural or material world as contrasted with things mental, or moral, or spiritual, or imaginary. Originally the word referred to all living things, including the human body, as well as to phenomena of the inanimate world. Later it took on more specialized meanings but always retained this twofold aspect, on the one hand relating to the inanimate world and on the other to the human body. We still find in Webster's dictionary two definitions of a physicist. The first definition given is "one versed in medical science." The second definition is "a specialist in the natural sciences." One who follows my profession of physicist is in France called a physicien, while in English the word "physician" means a medical practitioner. Similarly in Germany I would be called a physiker, whereas in English-speaking countries a physicker is one who administers a physic. But whereas those words which have the same original root have followed these two lines of continually narrowing significance, the progress of modern science is in many ways bringing the two together because on every hand the natural scientist is bringing more and more to the service of the physician his increasing knowledge and control of the materials and forces of nature.

The contributions of the sister sciences to medical science and art have in part been in the nature of tools and materials and in part been a better understanding of the fundamental structure and functioning of the human body. From physics, for example, have come such tools as the thermometer, stethoscope, electrocardiograph, x-ray, and a host of other devices ranging all the way from mere gadgets to highly complicated instruments. From the chemist have come such materials as most of the ordinary medicines and drugs in enormous variety, radium and synthetic vitamins. From the physiologist and biologist has come the more detailed knowledge of the structure and functioning of the human body. The psychologists are contributing their share in untangling the complicated relationship between mind and body.

The past history of the Rockefeller Foundation offers a good illustration of the importance which thoughtful students of medical science attach to the sister sciences. This foundation has always attached the greatest importance to the advancement of medical science. About twenty-five years ago, just after World War I, it came to the conclusion that a very important method for the long-term advancement of medical science was the more adequate support of research in the physical and biologic sciences, and this decision was implemented by the great program of National Research fellowships and of grants to support research in the various sciences. This and similar programs by various agencies have paid dividends in a large way, for out of such activities have come, in the past decade, such things as the sulfonamide drugs, DDT, synthetic vitamins, high voltage x-rays, various forms of radiation therapy, radioactive tracer studies and many other medical applications.

Out of this great variety of new contributions to medical science I would describe in brief detail just a few examples which seem to me to illustrate some of the more important trends and developments. These examples are chosen from activities with which I have had some direct or indirect contact, and I make no claim that they are selected with any priority of importance among many other illustrations which some one else would be better qualified than I to describe. However, they are certainly important and are indicative of the trend of things to come.

ARTIFICIAL LIMBS

To the uninitiated there would seem to be nothing new about artificial limbs. The genial ruffian John Silver in Robert Louis Stevenson's "Treasure Island" thumped around on an artificial leg. The more modern artificial legs are more shapely and are likely to have articulated joints. However, they have been far from adequate replacements for the functioning of the natural limb.

During the past war for the first time in history, so far as I know, there has been mobilized a cooperative organization composed of medical men, manufacturers of surgical equipment, physiologists, physicists, skilled instrument makers and inventors in an effort to bring all available knowledge and art to bear on the problem of

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creating artificial limbs which will as nearly as possible permit a crippled person to move, act and manipulate in normal fashion. Organized under the Office of Scientific Research and Development, this group is headed by Dr. Paul E. Klopsteg, a physicist, formerly head of the Central Scientific Company and now in charge of graduate study and research in the Technological Institute of Northwestern University. One problem has been the design of artificial legs which have joints with the proper combination of flexibility and stiffness at the appropriate angles to permit walking upstairs or downstairs. Another problem is the design of artificial hands which can be turned and whose fingers can be manipulated through cords attached to muscles in the stump. It is already evident that this combined effort is bringing about a very decided advance in the design of artificial limbs. Though instigated to meet one of the unfortunate conditions resulting from the war, it is a fact that the number of annual amputations resulting from accidents in peacetime considerably exceeds the number of similar war casualties, and it may therefore be said that the focusing of expert attention on this problem at this time should be reckoned as one of the useful results of the war.

SOME PROSPECTS IN BIOLOGY

My colleague Professor Francis Schmitt likens the present prospect in biology to that which faced the physicists and chemists in the early days of this century when it had been discovered that the atom, hitherto believed to be indivisible and in fact so named, had been proved to have a structure of electrical components held together by complex forces. First the exterior electronic structure of the atom and then the inner nucleus of the atom itself have been explored, and all the modern knowledge of spectroscopy, ionization, isotopes and atomic energy has developed with startling rapidity to usher in a new era of physical science. Similarly, the development of new experimental tools such as the ultracentrifuge, the electron microscope and the use of radioactive tracer materials is making possible a new type of quantitative biology far more powerful than the older descriptive biology and beginning to yield significant information regarding the ultimate constitution and fine structure of living matter. There is every reason to believe that these developments of quantitative biology are ushering in a new era for the understanding and ultimate control of fundamental life processes. Let me give a few illustrations which are suggestive of things to come.

Dr. Avery and his co-workers at the Rockefeller Institute have isolated nucleic acid from the capsule which surrounds the pneumococcus. There are several dozen strains of pneumococci and they seem to owe their specific characteristics to substances in the capsule. The capsule can be removed, leaving an organism which, though still alive, is avirulent until a new capsule is formed. If purified nucleic acid which has been isolated from one strain is added to the decapsulated cocci of another strain, the resulting bacteria show the genetic and pathogenic properties of the strain from whose capsules the nucleic acid was prepared. A predictable genetic mutation appears to have been produced. Geneticists have sought in vain to accomplish this in higher organisms. This is a model of the action of genes, which are also supposed to contain nucleoproteins. However, in the case of the capsule nucleic acid the material is a purified compound. The ability of viruses and cell constituents to reproduce themselves is closely correlated with the presence of nucleic acid. This experiment of Avery suggests that the nucleic acid, possibly in combination with a specific protein, acts like a gene.

In the last century it was supposed that enzymes could never be isolated in active form from living cells. Now we know that enzymes are protein molecules which can be isolated, purified and studied, physically and chemically. Will this history repeat itself in the case of genetic determiners, the genes? Will it be possible to determine genetic characters of forms higher than bacteria by administering isolated "genes" or gene activators representing such characters?

As another example, consider substances which have antibiotic action. There are certain substances which have no toxic effect on body cells but which inhibit the reproduction of micro-organisms. Under such conditions the organisms may increase in size but they do not reproduce. This has already had immense medical significance. Moreover, when the structure of a few antibiotics is known, as, for example, penicillin or streptomycin, the organic chemist may alter various groups in the molecules and hope to produce synthetic antibiotics for various diseases for which no natural antibiotic has yet been found.

Another example is the competitive inhibition of enzyme reactions. An enzyme has chemical groupings by which it can cause specific alterations in certain substrates. If a substance closely related to the specific substrate is added to the enzyme, the active groups of the enzyme combine with the substance and the enzyme is effectively poisoned. If the specific substrate itself is added, no reaction occurs. For example, there is an enzyme (cholinesterase) which splits acetylcholine, a powerful nerve stimulant and the hormone which produces smooth muscle contraction. If a tissue is treated with physostigmine, which contains a chemical group similar to that of acetylcholine, the enzyme is poisoned. Physostigmine has been used pharmacologically for years, but the mechanism of the action has only recently been discovered. Along this line a number of investigators have been trying the effect of a variety of compounds closely related chemically to the normal food substances used by bacteria in the hope that they may, by competing with these substances for the enzyme molecules, starve the bacteria to death.

A final example in this field is the development of new technics in the use of the electron microscope which make this instrument even more powerful in the study of biologic material. Fine structure in certain fibrous proteins has already been discovered and many protein molecules, such as the albumins, globulins and fibrinogen, in blood may soon be visualized directly. In the past these molecular shapes had to be deduced by indirect methods. Now that it is possible to visualize these molecules directly, a whole new era is opened up for the discovery of various biologic entities such as viruses responsible for certain diseases. By this means during the war the viruses of influenza were isolated and photographed, and their chemical composition has been determined.

Enzymes and chromosomes can now be observed directly with the electron microscope, and it appears possible thus to determine the physical basis of the gene mechanisms determining heredity.

By these illustrations I would not wish to imply that all these problems have been solved. What I wish to point out, however, is that new and very powerful technics of investigation have been developed sufficiently to offer a strong feeling of optimism that we are now on the threshold of a period in which knowledge of a most fundamental and important character will be secured in the realm of fundamental biology with applications to medicine.

It is this type of fundamental knowledge which probably forms the most promising basis of the great cooperative attack on cancer which is now being organized. A considerable portion of the funds collected by the American Cancer Society are scheduled for administration by the Committee on Growth of the National Research Council to mobilize all the resources of physics, chemistry and biology for this investigation. It is fortunate that those directing the use of the cancer money realize the importance of fundamental research if there is to be any hope of securing a really significant answer to the cancer problem or to any of the other complicated and obscure problems of disease and health.

SOME EXAMPLES FROM PHYSICAL SCIENCE

I have already mentioned important medical tools like the thermometer, stethoscope and x-ray, which have been contributed from the physical sciences and which are so widely used as to have become commonplace. However, there are new contributions at hand or in sight of great significance of which I shall give only a few illustrations.

Radium and x-ray therapy of cancer have been practiced for several decades. It is only about one decade, however, since the more penetrating x-rays produced at voltages of a million or more have become available for use as a by-product of the physicist's development of high voltage generators for experimentation on the artificial transmutation of atoms. There is still another exceedingly promising prospect involving a modification of this x-ray technic, however, namely the therapeutic use of the high speed electrons, or cathode rays themselves, instead of the x-rays which they would produce on striking the target of an x-ray tube. In other words, the proposal is to shoot the high speed electrons directly into the living tissue instead of irradiating this tissue with x-rays. In either case the biologic or therapeutic action is produced by the same mechanism, namely by the bombardment of the living cells by the secondary electrons produced within the tissues. As far as this therapeutic action is concerned, it makes no difference whether the secondary electrons have been set in motion by x-rays or by high speed cathode rays. However, it may make a great deal of difference to the patient because of a very curious characteristic of cathode rays as they pass through matter.

Cathode rays produce relatively few secondary electrons when they are moving with high speed, and they produce most of the secondary electrons after they have been slowed down and just before they have stopped in passing through the absorbing material. The significance of this fact in cancer therapy is suggested by the following example: Suppose that it is desired to treat a cancer which is located about 1 inch beneath the surface of the abdomen. Electrons or cathode rays produced by a 5 million volt machine are able to penetrate the body to a depth of about 1 inch. If these therefore are directed into the abdomen in the direction of the cancer to be treated, they produce few secondary electrons and therefore little biologic effect near the surface where they enter, but they produce the maximum number of secondary electrons and therefore deliver their maximum therapeutic dose at the depth of about 1 inch, just before they come to rest. This gives a method of concentrating a dose of therapy at any desired depth within the body with a minimum of erythema or biologic action in the path of entrance and with no biologic action in the region deeper than the desired location. The traditional method of x-ray therapy, on the contrary, has a disadvantage, as far as depth dosage is concerned, in that the maximum dosage is greatest at the point where the x-rays enter the body, and the dosage decreases with depth.

Of all the new physical-chemical tools, however, the one which seems to me to have the greatest promise in the medical field is the use of artificial radioactive substances, either as tracers or as therapeutic agents, and I would give two examples which are suggestive of a wide variety of applications on these matters.

Some ten or a dozen years ago Dr. Means and his colleague Dr. Hertz of the Massachusetts General Hospital and the Harvard Medical School became interested in the possibility of using radioactive iodine for the localized therapy of the thyroid gland, especially in cases of such a disorder as toxic diffuse goiter. They did this work in collaboration with Professor Robley Evans, who is in charge of the Massachusetts Institute of Technology cyclotron program and the outstanding scientist in this country in the use of radioactive tracer materials and the quantitative measurement of minute quantities of radioactivity.

Some experiments were first made to see how much iodine would be absorbed into the thyroid gland from the blood stream and how fast it could get there. The radioactive iodine was prepared with the cyclotron, and the early experiments were carried on by injection into rabbits. It was found that within about five minutes all the iodine that could be absorbed by the thyroid gland had been thus absorbed and that, in proportion to the size of the thyroid gland, from twenty to two hundred times as much iodine went to the thyroid gland as to any other organ or tissue of the body. If the rabbit had been on an iodine starvation diet, or if the rabbit had a case of spontaneous goiter, or if it was a pregnant female the higher values of iodine absorption in the thyroid gland were observed. All the quantitative measurements were made with the use of the Geiger counter, that marvelously sensitive instrument which, through ionization of the surrounding air, can detect the presence of radioactive iodine and measure its amount, atom by atom.

Later, similar experiments were carried on with human beings and they have been continued by Dr. Chapman, in collaboration with Drs. Means and Evans since Dr. Hertz entered the Navy early in the war. Having determined the quantities of iodine absorbed in the thyroid gland, the next step was to introduce quantities of radioactive iodine of sufficient amount to have localized therapeutic value because of the radioactive radiations admitted locally from the iodine right in the thyroid gland itself. I understand that upward

of two dozen patients have been thus treated with good results.

This is one illustration of the several possibilities which have been envisaged for the therapeutic use of radioactive materials which can be manufactured with the cyclotron and which have the characteristic of specifically large absorption in certain organs or tissues of the body.

My other illustration has to do with the use of radioactive chemical elements as tracer materials, in which their radioactive properties and their resultant capability of detection by a Geiger counter make it possible to determine accurately and quantitatively the location of these materials at any subsequent time. If, for example, one takes a drink of water containing a little ordinary salt whose sodium has been made radioactive in a cyclotron, it is possible with a Geiger counter to determine how soon this salt has passed through the walls of the stomach into the blood stream and reached any part of the body.

The most interesting recent example of this technic was in the studies of surgical shock and the development of technics for the preservation of whole blood for transfusion during the war. This work was carried on under a basic contract between the Committee on Medical Research of the Office of Scientific Research and Development and the Massachusetts Institute of Technology and was a cooperative enterprise involving also the Massachusetts General Hospital, the Harvard Medical School and the Peter Bent Brigham Hospital. The work was in charge of Dr. John Gibson, Dr. Joseph Aub and Professor Robley Evans. The program was supplemented by work also by Dr. Ross of the Evans Memorial Hospital, Dr. Denstedt of McGill University, Dr. Strumia of the Bryn Mawr Hospital and others, all of them utilizing the materials produced by the Massachusetts Institute of Technology cyclotron and the radioactive measurements by Professor Evans and his colleagues.

Radioactive iron was the material used because of its importance as a constituent of hemoglobin. Two types of radioactive iron were used, one manufactured with the cyclotron by bombardment of cobalt, and the other by the bombardment of manganese, and the two types could be distinguished in subsequent measurements by the fact that the former lost its radioactivity at the rate of one half in five years, and the other at the rate of one half in forty-seven days.

When experiments on blood transfusion were carried out, one of these radioactive forms of iron was injected into the recipient of the blood transfusion so as to tag his own red corpuscles, and the other type of radioactive iron was injected into the blood donor so as to tag the red corpuscles of the blood used in the transfusion. By this means one type served as the control and the other type served as the experimental blood donor source.

By these technics several extremely important investigations could be carried out. One had to do with the reaction of the various blood types on one another. It was possible, for example, to find out whether blood from a group O donor with a high anti-A titer, when transfused into a recipient with a different blood type, lost its potency in the presence of the second type, or vice versa. By this method some new discoveries were made regarding the interaction of blood types which greatly safeguarded blood transfusion and which have been proved to have application in certain situations in childbirth as well as in surgery.

But the greatest wartime contribution of this method was for determining the best methods for preservation of whole blood and for setting up the technical standards for the great blood donor program. By the device of using the tagged iron atoms in the donor's blood, direct evidence could be obtained regarding the potency of this blood after various durations of storage at various temperatures when admixed with various suggested preservatives. All that it was necessary to do at the end of any given storage period was to transfuse this blood into a recipient and shortly thereafter determine the amount of the donor's blood which still remained active in his blood stream. It was by this method that there was established the national standard specifying that after twenty-one days of storage at least 70 per cent of the transfused red cells must remain in circulation of the recipient for at least twenty-four hours.

GENETIC CHANGES

During the past decade or two an increasing amount of interest has been focused on the genetic changes which can be produced by x-ray or neutron radiations. The best known example is that of the drosophila or fruit fly, which, after exposure to x-rays, has a certain probability of producing new species characterized by red eyes or other new characteristics. One of the most interesting illustrations has been the production of new species of plants by strongly irradiating the germinating seeds with x-rays. In this way a new type of tobacco plant with a 13 foot leaf has been produced, as one of many examples of agricultural possibilities.

To the medical profession this phenomenon is of interest because of the possibility that by action of x-rays, neutrons or other high speed particles new types of biologic materials may be produced. These may be new types of dangerous germs, as, for example, new variations of influenza, or conversely they may be new types of beneficial medical material, derived, like penicillin or herb extractions, from living matter. Experiments have gone far enough to prove that there are possibilities along these lines and to suggest that there may here be an enormous field of importance to medical science of which we are just on the threshold.

This field was opened up by x-rays and cyclotrons. Probably the great uranium piles which have been designed in connection with the atomic bomb development and which give off enormous quantities of radiation may supply a new radiation tool for medical science. It may be possibilities of this general type which are suggested when we hear that the new developments in the production and control of atomic energy have potentialities in agriculture and medicine as well as in mechanical power and warfare.

CONCLUSION

I hope that these illustrations, selected more or less at random, may serve to suggest the possibilities which apparently lie ahead in the near future as goals for those scientists in the various fields who would cooperate with medical science in advancing our knowledge of living processes and developing still more powerful arts of medical science.